

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 May 2000 (03.05.00)	
International application No. PCT/GB99/02257	Applicant's or agent's file reference 92559/JND/CH
International filing date (day/month/year) 13 July 1999 (13.07.99)	Priority date (day/month/year) 13 July 1998 (13.07.98)
Applicant SCHMIDT, Günter et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

08 February 2000 (08.02.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02257

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H21/00 C12Q1/68 G01N33/58 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N C07H C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 118 605 A (URDEA MICHAEL S) 2 June 1992 (1992-06-02) column 10, line 32 - line 34 column 10, line 59 - line 63 claims 1,7,8 ---	1-3,7, 14-16, 32,33
X	F BERGMANN, W PFEIDERER: "21. Nucleotides. Part XLI. The 2-Dansylethoxycarbonyl (=2-{5-(Dimethylamino)naphthalen-1-ylsul fonyl}ethoxycarbonyl; Dnseoc) Group for Protection of the 5'-Hydroxy Function in Oligodeoxynucleotide Synthesis" HELVETICA CHIMICA ACTA, vol. 77, 1994, pages 203-215, XP002122219 page 203 --- -/--	1-16,32, 33,35-38



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 November 1999

Date of mailing of the international search report

09/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Hart-Davis, J

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/02257

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	F BERGMANN, W PFEIDERER: "92. Nucleotides. Part XLIII. Solid-Phase Synthesis of Oligonucleotides Using the 2-Dansylethoxycarbonyl (=2-[5-(Dimethylamino)naphthalen-1-ylsulfonyl]ethoxycarbonyl; Dnseoc) Group for 5'-Hydroxy Protection" HELVETICA CHIMICA ACTA, vol. 77, 1994, pages 988-998, XP002122220 page 991	1-16, 32, 33, 35-38
X	M R LEWIS, J E SHIVELY: "Maleimidocysteineamido-DOTA Derivatives: New Reagents for Radiometal Chelate Conjugation to Antibody Sulfhydryl Groups Undergo pH-Dependent Cleavage Reactions" BIOCONJUGATE CHEMISTRY, vol. 9, no. 1, January 1998 (1998-01), pages 72-86, XP002122221	1-3, 7, 14, 15, 20, 30-34
A	page 81; figure 9 page 82; table 4	17-19
A	US 5 216 141 A (BENNER STEVEN A) 1 June 1993 (1993-06-01) figure 6B	1
A	WO 97 27327 A (DARWIN MOLECULAR CORP ;TABONE JOHN C (US); MULLIGAN JOHN T (US); H) 31 July 1997 (1997-07-31) claims 33-61; figure 13 page 43, line 16 - line 18 page 43, line 24 - line 26	1, 20, 31
A	EP 0 596 355 A (GENENTECH INC) 11 May 1994 (1994-05-11) page 9, line 24 - line 31; example 5	1-15, 17-19, 32, 33, 35-38
A	WO 94 13319 A (HAEBICH DIETER ;MILES INC (US); BENZ GUENTER H H H (US); DREYER RO) 23 June 1994 (1994-06-23) figures 1A-1F; examples 2, 3	1-15, 17-19, 32, 33, 35-38

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02257

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ GB 99/02257

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15 (partially), 16, 30 (partially), 32-33 (partially), 35-38 (partially)

Method for characterizing an analyte using a compound of formula $R-SO_n-CH_2-R'$ ($n=1$ or 2) where one of R and R' comprises an analyte and the other comprises a reporter group, the link between them being cleavable to allow detection of the reporter group, wherein the analyte comprises a nucleotide, oligonucleotide or nucleic acid.

2. Claims: 1-15 (partially), 17-19, 30 (partially), 32-33 (partially), 35-38 (partially)

Method for characterizing an analyte using a compound of formula $R-SO_n-CH_2-R'$ ($n=1$ or 2) where one of R and R' comprises an analyte and the other comprises a reporter group, the link between them being cleavable to allow detection of the reporter group, wherein the analyte comprises an amino acid or peptide.

3. Claims: 1-15 (partially), 20-29, 30 (partially), 31, 32 (partially), 34, 35-37 (partially), 39

Method for characterizing an analyte using a compound of formula $R-SO_n-CH_2-R'$ ($n=1$ or 2) where one of R and R' comprises an analyte and the other comprises a reporter group, the link between them being cleavable to allow detection of the reporter group, wherein the reporter comprises a mass marker detectable by mass spectrometry.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02257

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AT 133714 T	15-02-1996
		AT 168724 T	15-08-1998
		DE 3854969 D	14-03-1996
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		EP 0360940 A	04-04-1990
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		ES 2083955 T	01-05-1996
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		JP 2676535 B	17-11-1997
		US 5258506 A	02-11-1993
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		JP 3505452 T	28-11-1991
		WO 8912060 A	14-12-1989
WO 9727327 A	31-07-1997	AU 1707997 A	20-08-1997
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		AT 119936 T	15-04-1995
		AU 616876 B	14-11-1991
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INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

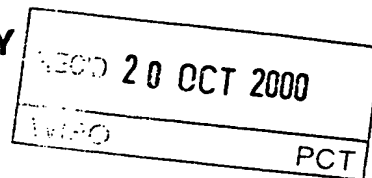
PCT/GB 99/02257

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0596355 A		NZ 223029 A	26-02-1990
WO 9413319 A	23-06-1994	AU 679675 B	10-07-1997
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		JP 8268911 A	15-10-1996
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		MX 9302725 A	31-08-1994
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		WO 9513084 A	18-05-1995

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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EE	Estonia	LR	Liberia	SG	Singapore		



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 92559/JND/CH	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/02257	International filing date (day/month/year) 13/07/1999	Priority date (day/month/year) 13/07/1998
International Patent Classification (IPC) or national classification and IPC C07H21/00		
Applicant BRAX GROUP LIMITED et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 8 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 08/02/2000	Date of completion of this report 19.10.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Gohlke, P Telephone No. +49 89 2399 8549 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02257

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-43 as originally filed

Claims, No.:

1-39 as originally filed

Drawings, sheets:

1/16-16/16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 48.3(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02257

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1, 2, 4, 5, 7, 14-16, 32, 33
Inventive step (IS)	Yes:	Claims
	No:	Claims 3, 6, 8-13, 17-31, 34-39
Industrial applicability (IA)	Yes:	Claims 1-34
	No:	Claims

**2. Citations and explanations
see separate sheet**

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section V:

- 1) Lack of novelty of claims 1, 2, 4, 5, 7, 14-16, 32 and 33:

Reference is made to the following document:

D1 = Helvetica Chimica Acta, vol. 77 (1994), pages 203-215.

D1 discloses the 2-dansylethoxycarbonyl group (Dnseoc) for protection of the 5'-hydroxy function in oligodeoxyribonucleotide synthesis. This Dnseoc group is 2-[5-(dimethylamino)naphtalen-1-yl]sulfonylethoxycarbonyl and thus comprises the linkage $-\text{SO}_2-(\text{CH}_2)_2-\text{OC}(\text{O})-$. It is easily cleaved with dilute DBU in aprotic solvents by β -elimination; the resulting 5-(dimethylamino)naphtalen-1-yl-vinyl sulfone can be **determined by UV detection at 350 nm or, more sensitively, by fluorescence detection at 530 nm** (see introduction part of D1, page 203). In the assembly of oligonucleotides using Dnseoc as 5'-protecting group, **the completeness of each coupling step can be checked by measurement of the absorbance at 350 nm of the eluate from the Dnseoc-deprotection** (see D1, page 206, lines 20-21); thus once the coupling step has been completed and once the Dnseoc group has been cleaved. The determination of condensation yields is also possible **by measuring the fluorescence at 530 nm** (see D1, page 206, line 22). In other words, D1 discloses a method for characterizing oligodeoxyribonucleotide being synthesized (= analyte), comprising

- providing said analyte protected at 5'OH position by a Dnseoc group (= group R comprising a reporter group), wherein the analyte is attached to the reporter group by the cleavable linker $-\text{SO}_2-(\text{CH}_2)_2-\text{OC}(\text{O})-$;
- cleaving the reporter group 5-(dimethylamino)naphtalen-1-yl-vinyl sulfone from the analyte with dilute DBU in aprotic solvent; and
- identifying the reporter group by UV at 350 nm or fluorescence detection at 530 nm, thereby characterising the analyte (in other words, gives an answer to the question whether the coupling step during oligonucleotide assembly has been completed or not).

According to D1 the covalent linkage attaching the analyte to the cleavable linker $-\text{SO}_2-(\text{CH}_2)_2-$ is a $-\text{O}-\text{CO}-$ group; and the R group comprises a naphthyl group between SO_2 and the reporter group; and the reporter group is a fluorescent label.

Therefore D1 anticipates the subject-matter of claims 1, 2, 4, 5, 7, 14-16, 32 and 33. Said claims do not meet the requirements of article 33(2) PCT.

However the particular embodiments of claims 3, 6, 8-13, 17-31 and 34-39 wherein specific groups adjacent to the $-\text{SO}_2-(\text{CH}_2)_2-$ linkage, are other than $-\text{O}-\text{CO}-$ group (see claims 3, 8-13, 17-19, 35-39); or the reporter group does not comprise a naphthyl moiety (claim 6); or the reporter group is a mass marker (claims 20-31, 34), are novel having regard to the available prior art.

2) Lack of inventive step of claims 3, 6, 8-13, 17-31 and 34-39:

Reference is made to the following documents:

D2 = WO 97/27327 (cited in the application as PCT/US97/01070)

D3 = US-A-5 118 605

D4 = BIOCONJUGATE CHEMISTRY, vol. 9, no. 1, January 1998 (1998-01), pages 72-86, XP002122221; M R LEWIS, J E SHIVELY: "Maleimidocysteineamido-DOTA Derivatives: New Reagents for Radiometal Chelate Conjugation to Antibody Sulfhydryl Groups Undergo pH-Dependent Cleavage Reactions".

It is generally known to the skilled man in the art that by investigating the detection of an analyte, the method employs a compound comprising said analyte attached to a label via a suitable cleavable linker, and comprises cleaving said cleavage site followed by detecting the presence of released label. In particular, in a method for assaying a nucleic acid analyte, suitable cleavage sites comprise a linkage selected from the group consisting of $-\text{CO}-\text{O}-(\text{CH}_2)_2-\text{O}-\text{CO}-$ (hydroxylamine-sensitive); $-\text{CO}-\text{NH}-$ (base-sensitive); $-\text{SO}_2-$ (base-sensitive); $-\text{S}-\text{S}-$ (thiol-sensitive); and $-\text{CH}(\text{OH})-\text{CH}(\text{OH})-$ (periodate-sensitive) (see for example D2 or D3).

More particularly, D2 discloses methods for characterizing a biological sample by detecting binding of ligand pair using non-fluorescent label; in other words the biological sample (and specifically nucleic acids) is cleavably linked to mass tag molecules (= reporter group), and then detected by mass spectrometry once the mass marker is being released. Suitable cleavable linkers are provided on pages 43-44 and include bis[2-(succinimidylloxycarbonyloxy)ethyl]sulfone (BSOCOES) comprising an

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB99/02257

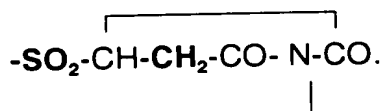
-SO₂-(CH₂)₂-OC(O)-O- linkage which gives a base-sensitive sulfone linkage. These suitable cleavage sites are also mentioned in **D3** (see column 10) relating in particular to methods for assaying a nucleic acid analyte.

However neither **D2** nor **D3** specifically exemplify an analyte attached to a reporter group by the cleavable linker BSOCOES.

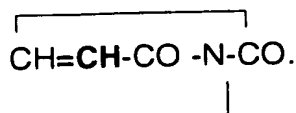
Having regard to this prior art, the problem to be solved by present application can be regarded as to provide a suitable cleavable linker for attaching an analyte to a reporter group, that cleaves without damaging associated analyte.

The solution proposed in present application cannot be considered as involving an inventive step for the following reasons:

D4 discloses maleimiocysteineamido derivatives of the macrocyclic chelating agent DOTA for labelling monoclonal antibodies with radiometals. In particular, **D4** provides maleimiosulfonylcysteineamido-DOTA (= MSC-DOTA = compound 3 in scheme 1, page 76) and its Yttrium chelate (= MSC-DOTA[Y(III)] = compound 12 in figure 8, page 81), both derivatives comprising the cleavage site -SO₂-succinimido-:



These conjugates undergo pH-dependent cleavage reactions by a **β-elimination reaction involving the sulfone group** and the **succinimide** group without evidence of metal ion dissociation during cleavage of the Yttrium chelate conjugate (see page 83, right column). The cleavage mechanism of MSC- DOTA[Y(III)] is indicated in figure 8, page 81 and results in the Yttrium chelate of DOTA-cysteinsulfenic acid (compound 13 (-SO₂H) and **maleimido** containing fragment



The subject-matter of present application differs from **D4** only in that claimed methods

employ a labelled analyte wherein the cleavage site comprises $-\text{SO}_2\text{-CH}_2\text{-CH}_2\text{-}$ instead of

$-\text{SO}_2\text{-CH-CH}_2\text{-}$. In fact, it is clear from D4 that the key- cleavage reaction is a β -elimination involving the sulfone group and the hydrogen at the C atom in the β -position to the SO_2 group (see figure 8).

Consequently, the linker $-\text{SO}_2\text{-CH}_2\text{-CH}_2\text{-}$ known as a suitable cleavable linker (see D1, D2 and/or D3) is merely one of several straightforward possibilities from which the skilled person would **select** without the exercise of inventive skill, as it is able to be cleaved by β -elimination involving the sulfone group and the hydrogen at the C atom in the β -position to the SO_2 group as explicitly taught by D1 and D4.

The **specific groups adjacent to the linker** $-\text{SO}_2\text{-CH}_2\text{-CH}_2\text{-}$ as defined in claims 3, 6, 8-13, 17-31 and 34-39 are known groups to any organic chemist for facilitating the necessary β -elimination reaction involving the sulfone group (= key-reaction). In other words it would be obvious to the person skilled in the art to apply these features as claimed in dependent claims 3, 6-13, 17-31 and 34-39, especially as the advantages thus achieved can readily be foreseen.

Therefore, **claims 3, 6, 8-13, 17-31 and 34-39** do not appear to fulfil the requirements of Article 33(3) PCT.

Section VII:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D3 and D4 are not mentioned in the description, nor are these documents identified therein.

Section VIII:

- 1) Claim 16: In the interest of clarity, it is requested to reformulate the compound claim of claim 16 into a method claim according to claim 15 (Article 6 PCT).
- 2) The wording "the content of prior art applications is incorporated by reference" found on page 15 should be removed from present application (Rule 9 (iv) PCT).

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- 3) The numbering of the prior art document GB 9826159.7 as referred to on page 25 needs to be rectified.